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INFECTIOUS MONONUCLEOSIS IN CHILDHOOD. A SURVEY OF 34 CASES

Special Report

Joseph M. LoPresti, M.D.

Paul Kaufman, M.D.

E. Clarence Rice, M. D.

This report represents a survey of thirty-four patients admitted to The Children's Hospital since January, 1935 with the diagnosis of infectious mononucleosis.

Infectious mononucleosis or glandular fever may be defined as an acute infectious disease of unknown etiology characterized by enlargement of the lymph nodes, characteristic changes in the white blood cells, a rising heterophile titer in some cases, and a uniformly favorable course.

In the selection of cases in this survey, three criteria were set up which are essentially the same as those utilized by Rapaport⁽¹⁾ in 1948 in his excellent monograph on this disease. To insure that the diagnosis in the selected cases was probably the correct one, certain modifications of these original standards were made:

1. Clinical manifestations which could all be explained by the diagnosis and which, usually, did not respond to the ordinary therapeutic measures.
2. A blood smear in which, at sometime during the illness, the lymphocytes were above 45 per cent and more than 10 per cent were atypical.
3. A positive heterophile agglutination with complete agglutination at a titer of 1:80 or above.

Many cases were excluded from this series because they did not fulfil any two of the given criteria.

Thirty-one of the thirty-four patients were admitted to the hospital in the last four year period. It is unlikely that this figure represents an increased incidence of this disease process in children. More than likely it reflects an increased index of suspicion on the part of the house and attending staffs.

There are conflicting reports in the literature concerning the seasonal incidence of infectious mononucleosis. In the four month period from January to April only five cases were hospitalized; while in the four month period from May to August, sixteen cases were admitted; and the remaining thirteen cases were hospitalized in the period from September to December (Table 1).

The definition of infectious mononucleosis gives no hint of the protean

forms in which it can exist, and new manifestations are still being recognized.⁽²⁾ Perhaps this disease entity is as great an imitator of other disease processes as syphilis. This becomes more apparent when our investigation reveals that twenty-three different conditions were suspected during the hospitalization of these patients (Table 2). Infectious mononucleosis per se was the initial diagnosis in 38 per cent (13) of the cases. The most

TABLE 1
Monthly Distribution of 34 Cases of Infectious Mononucleosis

MONTH	NUMBER	MONTH	NUMBER	MONTH	NUMBER
January.....	2	May.....	6	September.....	1
February.....	2	June.....	3	October.....	2
March.....	1	July.....	3	November.....	4
April.....	0	August.....	4	December.....	6
Total.....	5		16		13

TABLE 2
Suspected Diagnoses in 34 Children with Infectious Mononucleosis

DIAGNOSIS	NUMBER	DIAGNOSIS	NUMBER
Specific enteritis.....	14	Allergic state.....	2
Septicemia.....	11	Upper respiratory infection....	2
Tonsillo-pharyngitis.....	11	Mesenteric adenitis.....	1
Leukemia.....	7	Vincent's angina.....	1
Diphtheria.....	6	Gastro-enteritis.....	1
Tuberculosis.....	5	Rocky mountain spotted fever..	1
Blood dyscrasia.....	5	Febrile convulsion.....	1
Lymphogenous diseases.....	4	Nephritis.....	1
Pneumonia.....	3	Measles.....	1
Sickle cell anemia.....	3	Appendicitis.....	1
Meningitis.....	2	Syphilis.....	1
Malaria.....	2		

commonly considered pathological entities were: Typhoid fever and related specific enteritides, tonsillopharyngitis, septicemia, leukemia, diphtheria, tuberculosis, blood dyscrasias, and lymphogenous diseases. When a rash was present, measles, urticaria, and other allergic conditions were the admitting diagnoses. A voluminous literature is appearing describing central nervous system involvement in infectious mononucleosis. However, only two cases in this series were suspected of having central nervous system disease.

Twenty-three of our cases occurred in the one to seven year age group

and eleven between the ages of eight and thirteen years. The youngest was eleven months of age and the oldest was twelve and one-half years old. Nine of these children were colored and twenty-five were white. We do not feel that this distribution is significant since the white to colored patient ratio is about 2:1 at this hospital. In concurrence with many other investigators, twenty-seven of these children were males; a ratio of 3.9:1 (Table 3).

Despite the variable nature of infectious mononucleosis a rather consistent clinical picture was encountered. By far, four symptoms were prevalent: fever, sore throat, cervical adenitis, and anorexia. The occur-

TABLE 3

Age, Sex, and Racial Distribution in 34 Children with Infectious Mononucleosis

AGE	NUMBER	AGE	NUMBER
1-2 years	5	7-8 years	0
2-3 years	3	8-9 years	4
3-4 years	4	9-10 years	3
4-5 years	3	10-11 years	2
5-6 years	3	11-12 years	1
6-7 years	5	12-13 years	1
Total	23		11

	WHITE	COLORED	TOTAL
Male	20	7	27
Female	5	2	7
Total	25	9	34

rence of these symptoms in a child over one year of age should make one suspect the diagnosis. Of interest were two patients with adenitis elsewhere. One of these had an inguinal adenopathy of such degree that it interfered with walking; in the other, axillary adenopathy was so marked that venous obstruction was produced. A generalized rash, transient in nature, was present in three children. In two it was maculopapular in character; in the other, it was urticarial. Clinical icterus occurred on only two occasions. An acute surgical abdomen was suspected in one case because of the presence of pain. Attention is drawn to the fact that a generalized convulsion heralded the onset in only one patient even though fever of significant degree is invariably encountered (Table 4).

The febrile course in infectious mononucleosis is deemed worthy of dis-

cussion. In general it was found that the temperature curve was of an intermittent-remittent type. However, it finally returned to normal by lysis. In a small percentage of cases the fever ended by crisis. The height of the fever was quite variable and in some cases it spiked as high as 105.0 F. As to the duration of fever, the patients in this series seem to fall into two distinct groups. The first is that of short duration, lasting from four to ten days, (twenty-three patients fell into this category). The second is that in which fever persisted for more than two weeks. One patient had a temperature elevation lasting four days, and, in two patients, the fever persisted for four weeks (Table 5).

TABLE 4
The Symptomatology in 34 Children with Infectious Mononucleosis

SYMPTOM	NUMBER	PER CENT
Fever	34	100
Sore throat	17	50
Enlarged cervical nodes	15	44
Anorexia	12	35
Dysphagia	5	15
Cough	4	12
Rash	3	9
Nausea and vomiting	3	9
Irritability	3	9
Listlessness	3	9
Jaundice	2	6
Other enlarged nodes	2	6
Headache	2	6
Angioneurotic edema	1	3
Abdominal pain	1	3
Convulsion	1	3
Diarrhea	1	3

Again, the physical findings were usually constant. Most commonly the tonsils and/or pharynx were inflamed. All of the children had enlarged, tender cervical lymph nodes. In a large percentage a generalized, shotty, non-tender lymphadenopathy was noted. The spleen was palpably enlarged in 58 per cent (twenty). An hepatomegaly was recorded in twelve cases. Findings which are most frequently encountered are noted (Table 6). In two patients nuchal rigidity was of sufficient degree to warrant lumbar puncture. The examiners recorded mild jaundice on two occasions, but no further laboratory investigations of this phenomenon were carried out.

The most interesting clinical feature of this study was the appearance of the tonsils. Six patients had had a tonsillo-adenoidectomy before con-

tracting infectious mononucleosis. In twenty-four of the remaining twenty-eight, the tonsils were inflamed and in nineteen of these they were hypertrophic. An inflammatory exudate was present in sixteen; in five the exudate was patchy and, in eleven, there was a definite membrane present. This

TABLE 5
Duration of Fever in 34 Children with Infectious Mononucleosis

DURATION	NUMBER	DURATION	NUMBER
4 days	1	2 weeks	5
5 days	4	3 weeks	4
6 days	7	4 weeks	2
7 days	5		
8 days	3		
9 days	2		
10 days	1		
Total	23	Total	11

TABLE 6
Physical Findings in 34 Children with Infectious Mononucleosis

PHYSICAL FINDING	NUMBER	PER CENT
Cervical adenopathy	34	100
Generalized adenopathy	26	76
Inflamed tonsils	24	71
Splenomegaly	20	59
Hepatomegaly	12	35
Inflamed pharynx	9	26
Otitis media	5	15
Jaundice	2	6
Dyspnea	2	6
Nuchal rigidity	2	6
Rash	2	6
Abdominal pain	2	6
Cheilosis	1	3
Glossitis	1	3

membrane so closely resembled the one seen in diphtheria that three of the patients received diphtheria antitoxin on admission to the hospital (Table 7).

It was a surprise to note that most of the patients had a mild anemia. The average hemoglobin was 11.7 grams, and the average erythrocyte count was 3,800,000 cells per cubic millimeter. The thrombocyte count was within normal limits on all occasions. It is generally agreed that the

leukocytic picture is the most characteristic feature of this disease (Table 8). In twenty-six of the patients the initial leukocyte count was 5,000 to 15,000 white blood cells per cubic millimeter, and eleven of these had a normal leukocytic count on admission. Twenty children had a leukocytosis initially or at some stage during the disease. In fourteen instances a leukopenia became manifest during hospitalization. The most severe leukopenia was 2,900 cells per cubic millimeter, and the highest count was 26,800 cells per cubic millimeter. Kaufmann⁽³⁾ in a report of 144 cases of infectious

TABLE 7
*Appearance of the Tonsils in 28 Children with Infectious Mononucleosis**

APPEARANCE	NUMBER	PER CENT
Inflamed.....	24	86
Hypertrophic.....	19	67
Membranous exudate.....	11	39
Purulent exudate.....	5	18

* 6 children had a tonsillo-adenoidectomy before contracting infectious mononucleosis.

TABLE 8
The Leukocyte Count in 34 Children with Infectious Mononucleosis

LEUKOCYTES	INITIAL COUNT	HIGHEST COUNT
cu. mm.	number	number
Below 5,000	3	1
5,000-10,000	11	4
10,000-15,000	14	7
15,000-20,000	3	7
20,000-25,000	2	0
25,000-30,000	1	1

mononucleosis demonstrated the presence of an eosinophilia during the acute phase of the disease in 49 of the cases (34.0 per cent), and states that the presence of an eosinophilia of 4 to 10 per cent or slightly higher is another point in favor of the diagnosis of infectious mononucleosis. In concurrence with this report, a significant eosinophilia of 5 to 15 per cent was present in six of our cases.

A relative lymphocytosis was present at some time in every case. In none of these children was this less than 47 per cent. In twenty-seven patients it was between 60 and 90 per cent. Rapaport¹ has stressed the importance of repeated blood smears since the lymphocytosis is frequently of a transient nature. The typical blood picture may be therefore over-

looked. We wish to stress again that all cases were excluded from this series in which less than 10 per cent of the total leukocyte count were of the characteristic atypical lymphocytes found in this disease. These cells are larger than normal lymphocytes. The nucleus is lobulated and has a cloudy appearance. The cytoplasm is basophilic and vacuolated, and may be folded on itself^(4, 5, 6).

The heterophile agglutination test is remarkably specific for infectious mononucleosis. False positive reactions may occur if the patient has been given horse serum or parenteral liver extract, or if he has had infectious mononucleosis within the past year. This test is rarely positive in other diseases, but unfortunately is negative in at least 10 per cent or more of the cases of proven infectious mononucleosis. While the test may become positive in the first week of the disease, it usually does not do so until the

TABLE 9
Relative Lymphocytosis in 34 Children with Infectious Mononucleosis

PERCENTAGE OF LYMPHOCYTES	NUMBER
Less than 50	3
50-60	3
60-70	7
70-80	13
80-90	7
Over 90	1
Total.....	34

second or third week, and even may be delayed until the fourth week of illness. The majority of children in this series had only one blood sample examined for heterophile agglutinins and that in the first week of illness. Three patients had no Paul-Bunnell test performed. In the thirty-one examined, twenty-one were negative and ten were positive. One of the patients with a negative test in the fourth week of illness developed a titer of 1:56 in the fifth week. Of the patients with positive heterophile agglutinins, only one was positive in the first week. In no case was the titer below 1:112. The greatest titer was 1:1692. Most authorities agree that the Paul-Bunnell test will remain positive for many months, in some cases for as long as one year. Two children in this survey had follow-up agglutination tests. The first was a two year old white male who had an initial titer of 1:448 in the third week of illness. When repeated four months later, no agglutinins could be demonstrated. The second was a nine year old white male whose titer in the second week of illness was 1:1692. It was still positive seven months later in a dilution of 1:224.

It is not generally appreciated how often the liver is involved pathologically in this disease. This liver damage is present in over 90 per cent whether or not hepatomegaly and/or jaundice are present. Rapaport⁽¹⁾ detected altered liver function in seventeen of the nineteen patients in whom it was studied. De Marsh⁽⁷⁾ in 1947, found that some degree of hepatic dysfunction, as shown by the cephalin-cholesterol flocculation and/or the sulfobromophthalein excretion tests, was present in all nineteen cases of infectious mononucleosis that he studied. Gall⁽⁸⁾, in 1947, found some degree of interference with liver function in thirty-two of the thirty-four patients studied by him. Other authors have pointed out the similarity of infectious mononucleosis and infectious hepatitis⁽⁹⁾. Only two patients in our series were studied from the standpoint of liver pathology. In both cases the cephalin flocculation test was three plus.

TABLE 10

*The Heterophile Agglutination Test in 31 Children with Infectious Mononucleosis**

DURATION OF ILLNESS AT TIME OF TEST	RESULT	
	Positive	Negative
First week	1	14
Second week	8	1
Third week	1	3
Fourth week	0	3
Total	10	21

* 3 children had no Paul-Bunnell test performed.

It is generally recognized that glandular fever is one of the diseases in which a biologically positive serological test for syphilis may occur. This false positive reaction occurs in approximately 3 per cent of the patients. Of the sixteen patients in this series who were studied from this standpoint, two developed positive serological tests. The first was a nine year old white male who had a generalized urticaria at the onset of his illness. The heterophile agglutination titer was 1:1692. In the second week of illness the qualitative Kahn and Mazzini tests were positive, however, the quantitative Wassermann was negative. There was no further follow-up of this patient. The second was a two year old white male with a positive heterophile agglutination of 1:448. In the second week of illness the qualitative Kahn, Mazzini, and Wassermann tests were positive. The quantitative Kahn was 140 units and the quantitative Wassermann was positive in the first five tubes. An extensive workup was carried out. The maternal blood was studied for syphilis and found to be negative. Roentgenographic studies

of the patient's long bones were interpreted as normal. Spinal fluid obtained from lumbar puncture had a negative Wassermann test and a normal colloidal gold curve. Within six weeks and with no specific therapy, the serological test for syphilis had become negative.

Throat cultures were carried out in a number of these patients and in a majority only normal flora, e. g., *Neisseria catarrhalis* and *diphtheroids* were found. In only one instance was *Hemolytic streptococcus* the predominating organism. In three cases *Hemolytic staphylococcus* was isolated. *Escherichia coli* and *Pseudomonas aeruginosa* each were cultured on one occasion (Table 11).

Because of the complex differential diagnosis involved in establishing the presence of infectious mononucleosis, the children in this study had an extensive number of laboratory examinations in addition to those

TABLE 11
Results of Throat Cultures in 18 Children with Infectious Mononucleosis

ORGANISM	NUMBER	PER CENT
Normal throat flora	7	39
Streptococci		
Non-hemolytic	4	22
Hemolytic	1	6
Staphylococci		
Hemolytic	3	17
<i>Escherichia coli</i>	1	6
<i>Pseudomonas aeruginosa</i>	1	6

already mentioned. All of these were essentially normal and are shown in Table 12. There were three patients in whom bone marrow aspirations were performed. One showed hyperplasia of erythroblastic elements; another, an increased number of eosinophilic cells; and the last, a normoblastic hyperplasia. A lymph node biopsy was studied in one case. This revealed the follicular pattern to be preserved. There was a follicular hyperplasia and a prominence of the stroma and cells of the reticulo-endothelial type. Eosinophiles, while present, were not numerous. The bone marrow changes and lymph node findings could not be interpreted as pathognomic of any disease process. The current view seems to be that there is no increase in the erythrocyte sedimentation rate in infectious mononucleosis; however, in all five cases in whom this was studied there was a significant elevation (19 millimeters per hour to 38 millimeters per hour by the Landsteiner-Wintrobe method).

Up to the present time there is no specific therapy for this disease. Because of the possibilities of permanent liver damage or exacerbations of

hepatic dysfunction, the state of the liver should be considered in the management of infectious mononucleosis. Lessons recently learned about the management of infectious hepatitis might well be applied to infectious mononucleosis. Probably the most important principle in therapy is rest in bed or decided restriction of activity until hepatic function returns to normal. It is questionable whether an increased intake of protein and carbohydrate alters the course of involvement in a young person who has been taking an optimal diet. However, until more evidence is available, such a diet with vitamin supplements is advisable. The possible after-effects of this type of hepatitis, e. g., increased vulnerability of the liver to malnutrition and intoxication, cannot be excluded.

TABLE 12

*Results of Other Laboratory Procedures in 34 Children with Infectious Mononucleosis**

LABORATORY PROCEDURE	NUMBER
Urine analysis.....	34
Tuberculin skin test.....	24
Febrile agglutinations.....	14
Blood cultures.....	11
Chest X-rays.....	11
Sedimentation rates.....	5
Sickle cell preparations.....	3
Bone marrow biopsies.....	3
Spinal fluid examinations.....	2
Malarial blood smears.....	2
Agglutination for tularemia.....	2
Lymph node biopsy.....	1
Agglutination for Rocky Mountain Spotted Fever.....	1
Electrocardiogram.....	1

* All the above examinations were negative or normal except the sedimentation rates.

Twenty-five of the patients studied received specific antibiotic therapy. The various drugs utilized were sulfadiazine, penicillin, streptomycin, aureomycin, chloramphenicol or a combination of these therapeutic agents. There was no apparent difference in response between the patients who received specific therapy and those in whom the therapeutic regime included only symptomatic and supportive measures. A few scattered reports are now appearing in the literature concerning the efficacy of aureomycin and chloramphenicol in the management of these patients. Three of our patients received aureomycin and two were treated with chloramphenicol. A short summary of these cases follows:

Case 1: A. A., a four year old white male was admitted on May 27, 1949

with a three week history of fever, sore throat, and cervical adenopathy which had not responded to penicillin therapy at home. Physical examination revealed a temperature of 102.4 F. There was a generalized lymphadenopathy. The tonsils were injected, hypertrophic, and covered with a purulent exudate. The spleen was palpated 8 centimeters, and the liver 2 centimeters below the costal margins. The white blood count was 7,000 cells per cubic millimeter with 62 per cent lymphocytes. The throat culture, skin test for tuberculosis, and heterophile agglutination test were all normal. The patient received 250 milligrams of aureomycin by mouth every four hours for twenty-four hours, and 250 milligrams every six hours for the next five days. The temperature returned to normal thirty-six hours after admission which, however, was three weeks after the onset of illness.

Case 2: H. F., a three year old colored male was admitted on December 17, 1949 with a three day history of sore throat, fever, and swollen cervical lymph nodes. There had been no response to penicillin therapy prior to hospitalization. On examination the temperature was 101.2 F. There was marked cervical lymphadenopathy and a generalized, shotty enlargement of the lymph nodes. The tonsils were inflamed, hypertrophic, and covered with a yellow, purulent exudate. The tip of the spleen was palpable. The heterophile agglutination test, serological tests for syphilis, throat culture, and tuberculin skin tests were all normal. The leukocyte count was 12,100 cells per cubic millimeter with 59 per cent lymphocytes of which 22 per cent were atypical. On admission this patient received 20,000 units of diphtheria antitoxin. On the second hospital day aureomycin therapy was instituted. He received 125 milligrams by mouth six hours for six days. The temperature returned to normal on the fourth hospital day, seven days after the onset of illness.

Case 3: J. A., a ten year old white male was hospitalized on May 22, 1949 with an eight day history of fever, sore throat, and a swollen neck. Penicillin had been utilized with no response before admission. Physical examination revealed a temperature of 104.0 F. and the patient was quite toxic. The tonsils were inflamed, enlarged, and covered with a grayish-white membrane. Marked cervical and generalized lymphadenopathy were present. The white blood count was 17,600 cells per cubic millimeter with 77 per cent lymphocytes of which 22 per cent were atypical forms. The blood and throat cultures were negative. There were no agglutinins for tularemia. The Paul-Bunnell test was positive through a dilution of 1:112. This patient received 40,000 units of diphtheria antitoxin on admission. Aureomycin therapy was instituted on the second hospital day. He received 1,000 milligrams by mouth every hour for four doses and then 500 milligrams every four hours for the next three days. This was reduced to 250 milligrams

every four hours for one day and, finally to 250 milligrams every six hours for two days. The patient's temperature returned to normal three days after aureomycin therapy was instituted. However, this was eleven days after the onset of illness.

Case 4: J. S., an eleven month old white male was admitted to the hospital on November 16, 1949 with a five day history of fever and sore throat. There had been no response to previous therapy with penicillin. On physical examination the temperature was 101.2 F. The tonsils were inflamed, hypertrophic, and covered with a greenish-yellow membrane. The cervical lymph nodes were enlarged and tender. The leukocyte count was 13,000 cells per cubic millimeter with 53 per cent lymphocytes of which 15 per cent were atypical. The heterophile agglutination test and throat culture on admission were normal. Oral chloramphenicol in a dosage of 250 milligrams every four hours was instituted on the second hospital day and continued for three days. The temperature returned to normal in twelve hours. This was seven days after the onset of illness.

Case 5: J. C., a three year old white male was admitted on January 2, 1950 with a nine day history of fever, anorexia, listlessness, and dyspnea. At home there had been no response to penicillin and sulfadiazine therapy. Examination revealed a temperature of 105.0 F. and the patient appeared toxic. In addition to a left otitis media, marked cervical adenopathy and a mild generalized lymphadenopathy were noted. The tonsils were markedly inflamed. The liver was palpated 6 centimeters below the right costal margin. The white blood count was 7,000 cells per cubic millimeter with 47 per cent lymphocytes of which 11 per cent were atypical. Blood cultures, febrile and heterophile agglutination tests, and lumbar puncture failed to reveal any abnormalities. On the third hospital day the patient was placed on chloramphenicol therapy. He received 125 milligrams orally every four hours for five days and 250 milligrams every six hours for the following two days. The temperature did not return to normal until four days after chloramphenicol was started.

It is obvious from the five cases presented that no definite conclusions can be drawn as to the efficacy of aureomycin and chloramphenicol in the treatment of infectious mononucleosis. It is best not to include these drugs as specific therapeutic agents in the management of this disease entity until a large series of cases has been treated early in the illness.

SUMMARY

A survey of thirty-four patients admitted to the Children's Hospital of Washington, D.C. since 1935 with the diagnosis of infectious mononucleosis was made.

This disease occurs most commonly in males, a ratio of 3.9:1 in this series.

A rather consistent clinical picture was encountered. Fever, sore throat, cervical lymphadenopathy, and anorexia were the four most prevalent symptoms. The most common physical findings were inflamed tonsils and/or pharynx; enlarged, tender cervical lymph nodes; a generalized lymphadenopathy; splenomegaly; and hepatomegaly. In eleven of the children a definite membrane covered the tonsils.

The positive laboratory findings revealed a peripheral leukocyte count which varied from a moderate leukopenia to a moderate leukocytosis. Six of the patients had a significant eosinophilia during the acute stage of illness. The heterophile agglutination test was positive in a titer of over 1:80 in 10 of the patients.

The frequency of hepatic involvement in infectious mononucleosis has been stressed and should always be considered in the management of this disease.

The present day status of aureomycin and chloramphenicol as specific therapeutic measures for infectious mononucleosis is felt to be in too early a stage of development for adequate evaluation.

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REFRACTORY MEGALOBLASTIC ANEMIA

Case Report No. 185

Joseph A. Rothschild, M. D.

A six week old colored male was admitted to Children's Hospital on December 14, 1949 with a history of two weeks duration of coryza and cough; and with a diarrhea of four to five loose, yellow-green, stools for one week prior to admission. For two days there was a history of vomiting of three to four times daily.

The past history was of a normal prenatal and neonatal course. The infant weighed five pounds, seven ounces at birth, and had gained weight progressively from that time until one week before hospital admission. His diet had consisted of adequate amounts of evaporated milk formula, orange juice, and cod liver oil.

Admission examination revealed a weight of five pounds, six ounces and a temperature of 99.0 F. Other than marked dehydration there were no positive findings. The liver and spleen were not palpable upon this examination or at any other time during hospitalization.

With electrolyte-fluid therapy the patient was easily hydrated. After one day, oral alimentation was begun with evaporated milk formula, cereals, etc. During the hospital course a progressive weight gain was maintained, until at the time of discharge on February 13 the weight was ten pounds, twelve ounces.

Laboratory work consisted of negative results on serological tests for syphilis, urinalysis, stool cultures and sickle cell preparations. Admission blood work revealed: red blood cells, 2,800,000 per cubic millimeter; hemoglobin, 9.2 grams per cent; and white blood cells, 10,000 per cubic millimeter, with an essentially normal differential count. Platelets were considered to be average in number. There were three nucleated red blood cells per 100 white blood cells. The erythrocytes showed a normochromia, with many macrocytes in the peripheral blood smear. On December 19, 1949 a bone marrow biopsy was done which revealed an erythroid-leukoid ratio of 1:1, with normal appearing myeloid elements, and a marked erythroid hyperplasia of a megaloblastic type. Twenty per cent of the immature red blood cells were megaloblasts.

The volume of packed cells was 29 cubic centimeters per 100 milliliters. The leukocytes on twenty-seven separate counts during the hospital course varied between 5000-15400 per cubic millimeter, with a mean average of approximately 9000 per cubic centimeter. No thrombocytopenia was noted at any time during hospitalization.

On December 20, 1949 medication of B₁₂ (Raubramin, Squibb) fifteen micrograms intramuscularly every other day was begun. The results are tabulated below. With this apparent therapeutic failure, on December 31, 1950 a blood transfusion of 30 cubic centimeters of whole blood was given. On January 2, 1950 Elixir Feosol was begun, and continued until January 4, 1950.

Another course of B₁₂ therapy was initiated on January 7, 1950, and continued for a period of two weeks. Here, again, the reticulocyte count was not dramatic. However, two things are to be noted. First, there is a slowly progressive rise of the erythrocyte picture, and secondly bone marrow studies done at the beginning and at termination of therapy did show improvement. (On January 12, 1950 a serum protein level showed total protein of 6.73, with a normal A:G ratio.)

On January 23, 1950 folic acid therapy was initiated in a dosage of 10 milligrams twice a day for a period of fourteen days. Serial bone marrow studies were performed as tabulated below. Here, again, throughout the course of treatment there was a progressive response as evidenced by the bone marrow smears. The reticulocyte count was not remarkable as noted on the table. Yet at termination of folic acid injections, the bone marrow on two to three occasions was of the nature that the diagnosis could no longer be made from it.

In order to exhaust the agents that might give a reticulocyte response, liver extract treatment in doses of fifteen units every other day for a period of ten days was then given. The response was not gratifying in the peripheral blood. But a repeat bone marrow smear on February 14 showed still further regression (Table I).

Because the patient had a normal bone marrow, and the erythrocyte and hemoglobin levels were adequate, he was discharged on February 13, 1950 to be followed in hematology clinic.

In the past four years, following the reports of Zeulzer and Ogden, and of Amato, a classical clinical and hematological syndrome has been found establishing the entity of (*Megaloblastic Anemia of Infancy*.)

Megaloblastic Anemia occurs predominantly in the white race. The characteristic age of onset is between three to twenty-one months, with a peak incidence of nine to twelve. Until the time of this writing (February, 1950) only one case had been described in a negro infant. Zuelzer describes a peculiar increased incidence in the fair, blond infants with blue eyes.

The etiology is not definitely established. Growth, diet and infection are of apparent importance.

1. Because of the onset in a period of very rapid growth, and because this disease occurs earliest in premature infants, growth and rate of growth are considered of importance.

TABLE I
Peripheral Blood and Marrow Response to Therapy

DATE	R.B.C.	HGB	RETICS	MARROW
Rubramin $\frac{1}{2}$ cc. every other day (From 12-20-49 to 12-31-49)				
12-20	2.8	7.5	7.2	Leukoid-Erythroid ratio 1:1; 20 meg/100 immature R.B.C.'s
12-21	2.8	8.8	5.3	
12-22				
12-23	3.4	8.9	4.4	
12-24	2.1	8.8	6.4	
12-25				
12-26		8.5	3	
12-27		8.3	4	
12-28		8.2		
12-29		9.0	7.8	
12-30	2.5	8.0	5.5	
12-31			7.0	
Rubramin $\frac{1}{2}$ cc. every other day (From 1-5-50 to 1-21-50)				
1-7				Leukoid-Erythroid ratio 1:1; 7 meg/100 immature R.B.C.'s
1-8	3.2	9.8		
1-9			0.9	
1-10			0.5	
1-11		10.2	2.4	
1-12			1.0	
1-13		9.4	1.3	
1-14			1.0	
1-15	3.7			
1-16			0.5	
1-17	2.9	9.5	0.5	
1-18			0.2	
1-19	3.8	10.1	1.2	
1-20			1.2	
1-21	3.7	8.9	0.5	
Folic Acid 10 mgm twice daily (From 1-23-50 to 2-4-50)				
1-23	.8	3.7	10	(10 hrs.) Leukoid-Erythroid ratio 3:1; 5 meg/100 immature R.B.C.'s
1-24	2.0	4.3		(24 hrs.) Leukoid-Erythroid ratio 24:1; 4 meg/100 immature R.B.C.'s
1-25	.8	3.2	9.7	Leukoid-Erythroid ratio 6:1; 5 meg/100 immature R.B.C.'s
1-26	.2	4.0	9.9	
1-27	2.8	3.6	9.0	
1-28	1.9	4.0	9.9	
1-29	1.3			
1-30	1.1	3.9	10	
1-31	1.1	3.6		
2-1	4.1	3.9	10	
2-2	2.0	3.7		
2-3	2.2	3.3	9.8	Leukoid-Erythroid ratio 4:1; 1 meg/100 immature R.B.C.'s

TABLE I—*Concluded*

DATE	R.B.C.	HGB	RETICS	MARROW
Liver Extract (From 2-4-50 to 2-14-50)				
2-4	2.4	4.3	7.8	Leukoid-Erythroid ratio 6.5:1; .3 meg/100 immature R.B.C.'s
2-5				
2-6				
2-7	2.8			
2-8	2.4	3.3	10	
2-9	.5			
2-10	1.9	3.3	9.8	
2-11	1.8	3.2		
2-12				
2-13				
2-14				

2. Several considerations of the role of diet in the etiology have been made, but nothing of a definite nature can be said. There have been reports in the literature concerning a striking correlation between the development of megaloblastic anemia and the intake of various forms of powdered milk simulating mother's milk. Vitamin C deficiency is another consideration. Thus far, the literature on the subject is sparse. Nothing of consequence has been written of its role as an etiological agent. It may be said that Vitamin C has not been of therapeutic value when used alone on the few cases who have had a therapeutic trial.
3. Because of the almost invariable onset of megaloblastic anemia of infancy with a respiratory infection or gastroenteritis, infection is considered of importance as an etiological agent. Any one, or any combination of the above mentioned factors are of etiological importance. There is, however, still the lack of a plasma factor in the etiology which is unknown. One experiment which substantiates this is the demonstrating of a failure to arrest the progress of megaloblastic anemia with washed red blood cells.

The typical onset of megaloblastic anemia of infancy is characterized by a duration of a few days of respiratory infection or gastroenteritis. The infection, being rarely severe, does not vary directly in severity to the degree of anemia. On examination, an infant is found who is usually underweight and pale. Occasionally petechiae are found. In approximately 50 per cent of the cases a palpable liver is found; in a slightly lower percentage of cases a palpable spleen is found.

The average range of hemoglobin reported is 4-6 grams per cent, with red blood cells between 1-2 million per cu. milliliter. The anemia is often

macrocytic and normochromic. It may be normocytic with a variable number of interspersed macrocytes. On rare occasions megaloblasts are found in the peripheral blood. Most often there is a leukopenia with neutropenia and thrombocytopenia. The serum protein is often below normal. Zeulzer reported an achlorhydria in $\frac{3}{4}$ of the cases in one series. Siebenthal reports that all patients in his group had a deficiency in gastric hydrochloric acid. It should be remembered, with the frequency of infections at the onset of this disease, that with virtually all infections in infants there is a decrease in stomach secretion of its acid.

It may be stated categorically that the diagnosis cannot be accurately made without a bone marrow biopsy. Examination of the marrow reveals a megaloblastic dysplasia. Many of the cells are described as intermediate between megaloblasts and normoblasts. This is a picture which simulates pernicious anemia.

There are some striking differences between the clinical pictures of pernicious anemia and megaloblastic anemia.

1. There have been no reported abnormal neurological findings in megaloblastic anemia of infancy.
2. Megaloblastic anemia does not require prolonged therapy. There are no reports of remissions of megaloblastic anemia once the bone marrow and hematological pictures have been reverted.
3. There is a resistant achlorhydria in pernicious anemia, whereas in megaloblastic anemia of infancy free gastric hydrochloride is found following therapy.

A chronological review of the therapeutic measures which have been developed for macrocytic anemias shows that in 1928 refined liver was first used, followed by the first usage of folic acid in 1945, and of vitamin B₁₂ in 1949. This is mentioned because, with early enthusiasm, it was thought that vitamin B₁₂ would replace use of the older drugs. All three still have a place in our armamentarium. There are case reports of failure to respond to Vitamin A, with a subsequent response to another drug substituted. From most reports, however, response to any of these agents is gratifying. It is an unusual case which is refractory.

With successful treatment with any of the three drugs, there are very significant bone marrow changes within 12 hours. Usually within 36 hours after therapy has been initiated, it is almost impossible to make a morphological diagnosis on bone marrow smear. In one series reported by Zuelzer, Newhall, and Huttaff, all megaloblasts were gone from the marrow of all patients within 96 hours.

With an adequate dose of folic acid, there is a maximum reticulocyte response, according to most reports, after 5 days (20-25 per cent reticulocytes). A significant rise in reticulocytes occurs on the third day. The same

is true of liver extract and vitamin B₁₂. However, the maximal reticulocyte count may be one to two days later.

The case presented is of interest for several reasons. Primarily, it demonstrates refractoriness in this disease (which we believe to be the same described as Megaloblastic Anemia of Infancy) to the usually successful methods of therapy. Despite the fact that there was thought to be no specific response to any one agent used, there was a steady progressive improvement in erythrocyte elements with all methods of therapy. The latter cannot be satisfactorily explained. Even though a normal bone marrow was found following folic acid, credit cannot be given entirely to that drug. Arrest of progression of the disease and hematological and clinical improvement was made before folic acid was used.

Other interesting aspects of the case are:

1. It is one of the youngest cases reported.
2. It is the second case found in the literature of Megaloblastic Anemia of Infancy in a Negro.

SUMMARY

1. A case of Megaloblastic Anemia of Infancy is presented in a Negro who was admitted to the hospital at 6 weeks of age.
2. Refractoriness in dramatic therapeutic response to simultaneously administered vitamin B₁₂, small blood transfusion, folic acid, and liver extract is demonstrated.
3. General characteristics of the disease are discussed.

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ADDENDUM

Some newer data appearing since this article was written shows that megaloblastic anemia was produced in monkeys fed diets adequate except for vitamin C (by May, Nelson, and Salmon).

Diamond says: "There is no response to Vitamin B₁₂ unless Vitamin C is also administered."

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A CASE OF ACUTE PHOSPHORUS POISONING WITH RECOVERY

Case Report No. 186

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J. B. 50-1921

J. B., a three year old white male was admitted to the Children's Hospital on February 12th, 1950. He was apparently well until the day of hospitalization when, between 8 and 10 A.M., he ingested rat poison. The ingested material was in the form of a paste spread on crackers and placed on the floor. The contents of the paste were $2\frac{1}{2}$ per cent phosphorus and $97\frac{1}{2}$ per cent inert ingredients. The child had evidently scraped part of the paste from one of the crackers. Although it was not definitely known how much he had ingested, the amount was thought to have been approximately one cubic centimeter. As soon as the accident was discovered the child was given warm milk "to make him vomit". He vomited two times that morning and six to ten times that afternoon. The vomitus was described as having a foul odor. The patient was admitted to the hospital approximately eight to nine hours after having ingested the rat poison. In view of the long time interval prior to hospitalization and the continuous vomiting, gastric lavage was not performed.

Physical examination revealed a well-developed, well-nourished white male who was drowsy but not acutely ill. The breath had a foul odor. He complained of slight abdominal pain. The rectal temperature was 99.6 F., pulse 120 per minute, and respirations 20 per minute. The skin was of normal temperature and color. There was moderate hypertrophy of the tonsils with mild injection of the pharynx. The heart was not found to be enlarged and no murmurs were heard. In spite of the complaint of abdominal pain, the abdomen was soft and no tenderness was present. The liver was palpated two centimeters below the right costal margin. The remainder of the physical findings were within normal limits.

The admission and subsequent laboratory data are given in the accompanying tables (Tables 1 and 2). These determinations aided in the course of therapy followed, which was mainly of a supportive nature. Treatment included: daily intravenous infusions of 500 cc. of 5% glucose in Hartmann's solution with Vitamins B and C included; Cal-Glucon tablets (1.5 grams) one orally, three times a day; one ampoule of Hykinone, (4.8 mgs.), and one milliliter of crude liver extract intramuscularly daily. The patient was placed on fat-free high carbohydrate diet.

Shortly after admission, he received an intravenous infusion of 500 milliliters of 5 per cent glucose in Hartmann's solution with 10 milliliters

of 10 per cent calcium gluconate added. During the night, the child vomited three times, but retained some saline-glucose-orange juice mixture. The following morning, the carbon dioxide combining power was found to be 27 volumes per cent. The acidosis was corrected with one sixth molar lactate administered intravenously. The next day the patient had stopped vomiting and his oral fluid intake was adequate. The liver was then palpable four centimeters below the costal margin, an increase of two centimeters since admission. It was very firm in consistency, possessed a sharp edge, but was not tender. A transfusion of 300 milliliters of whole blood was given on this day. On the fourth hospital day, the sclerae were noticed to have a yellow tint, and the skin was icteric. The liver had increased in size and was six centimeters below the costal margin. On the following day, 500 milliliters of protein hydrolysate in 5 per cent glucose were given intravenously. A reaction of nausea and vomiting occurred. The adminis-

TABLE 2

DAY OF ILLNESS	HEMOGLOBIN	ERYTHROCYTES	LEUKOCYTES	NEUTROPHILS	LYMPHOCYTES	EOSINOPHILS	MONOCYTES
	gms.			%	%	%	%
2	11	3.3 million	7,000	60	40		
6	14	5.2 million	5,000	44	45	6	5
20	11	3.5 million	7,700	47	50		
26	9.5	2.9 million	8,900	54	45		
27	12.5	3.9 million	6,500	53	44		

Shick; Serology; Old Tuberculin—all negative.

tration of this fluid was not repeated. On the sixth hospital day, the liver was noted to be tender for the first time. The general condition of the patient was unchanged. A low grade fever had persisted from the third hospital day.

The rectal temperature spiked to 104.0 F. on the seventh day. Examination revealed the liver to be slightly larger, the jaundice was still present, and the pharynx injected. Procaine penicillin, 300,000 units intramuscularly twice daily was instituted. During the next two days, the rectal temperature spiked to 103.2 and 102.0 F. respectively. The liver edge was palpable at the umbilical level. The temperature gradually receded during the following week. The patient seemed to feel better, and his oral fluid intake was adequate. The liver slowly decreased in size and gradually became less firm and non-tender. An electrocardiogram obtained on the sixteenth hospital day was within normal limits. On the seventeenth day of hospitalization the liver edge was palpated four centimeters below the costal margin. It was of normal consistency. Jaundice could not be detected clinically.

The rectal temperature had not been over 100 degrees for four days. The penicillin was discontinued. The remainder of the hospital course was uneventful. A hemogram on the twenty-sixth day revealed a mild anemia. A transfusion of 300 milliliters whole blood was given, and the patient was discharged on the following day. Since then the patient has been followed in the Out-Patient Department.

DISCUSSION

As little as 15 milligrams of yellow phosphorus will produce symptoms of poisoning. In acute phosphorus poisoning, severe, burning abdominal pain, nausea, and vomiting may occur immediately on ingestion or be delayed for several hours. The breath and vomitus possess a garlic odor, and the vomited fluid may be luminous. Death occurs from shock. If the patient survives the acute phase, a period of one to three days passes before the toxic effects of phosphorus upon the liver, heart, and glands become manifest⁽¹⁾.

A series of fourteen patients has been reported⁽²⁾ with acute phosphorus poisoning in which there was a 50 per cent mortality rate. The commonest source of phosphorus as a poison is in the proprietary rat poisons and roach and vermin powders. The signs and symptoms of acute phosphorus poisoning are classically divided into three stages:

1. The first stage begins shortly after the ingestion of the poison. The symptoms are those of acute gastro-enteritis. An odor of garlic of the breath and vomitus is an extremely valuable sign, as it is practically pathognomonic of phosphorus poisoning. This stage usually lasts six to eight hours.

2. The second stage is a symptom-free period, usually lasting from one to three days, and occasionally as long as ten days.

3. The third stage is characterized by systemic toxemia due to the action of the absorbed poison. The liver enlarges rapidly, becomes tender, and icterus develops. Massive hematemesis and hemorrhage into the skin, mucous membranes, and viscera may occur. Renal damage is evidenced by oliguria, hematuria, and casts. The electrocardiogram shows changes in the T wave and S-T segments of leads 1, 2, and 4⁽³⁾. Death may be due to profound irreversible hepatic failure, central nervous system damage, or massive hematemesis.

Recovery or death may occur in either stage one or stage three, although recovery from stage three is unusual.

In the case reported, it was estimated that about 25 milligrams of yellow phosphorus was ingested. The course of the patient closely followed the three clinical stages described above. The second stage was represented by the asymptomatic third hospital day. Following this asymptomatic period, the liver enlarged, became tender, and icterus developed—indicative of the

third stage. However, hematemesis and other hemorrhages were not present. Microscopic examination of the urine showed a few white blood cells, red blood cells and casts on the sixth, seventh, and eighth hospital days. The electrocardiogram was within normal limits. During the remainder of the hospital stay, gradual clinical improvement was noted. This was substantiated by the return to normal of various liver function tests. The prothrombin time, icterus index, and cephalin flocculation returned to a normal level, and the bilirubin disappeared from the urine. It is interesting to note that the thymol turbidity test became elevated on the seventeenth day and remained elevated through the forty-first day of illness. This persistent elevation of the thymol turbidity and the increase of urobilinogen in the urine in the later part of the patient's illness are strong indications of continued liver dysfunction.

Another point of interest in the case presented is that the patient had an inorganic phosphorus blood level of 2.4 milligrams per cent on the fifth day of illness. This was repeated on the forty-first day of illness and was found to be 4.6 milligrams per cent. Other authors have reported low phosphorus levels in phosphorus poisoning. The patients of Rubitsky and Myerson⁽³⁾, Blumenthal and Lesser⁽⁴⁾, McIntosh⁽⁵⁾, and McLean and his associates⁽⁷⁾, had blood phosphorus levels of 2.96, 2.2, 3.4, and 2.7 milligrams per cent respectively. None of these patients had any evidence of rickets. One of these authors expressed the view that these low phosphorus levels might be due to an inability of the body to metabolize carbohydrates properly⁽⁷⁾.

A case of acute phosphorus poisoning has been reported⁽⁵⁾ in which X-rays of the long bones seven weeks after ingestion were negative. However, four months later roentgenography revealed a phosphorus band proximal to the epiphyseal lines. These bands were still visible roentgenographically fourteen months after poisoning. In our case, X-rays of the long bones obtained on the twenty-sixth hospital day showed no evidence of bone pathology. Repeat X-rays on the forty-first day of illness revealed phosphorus bands in all of the long bones (Figs. 1-3).

The treatment of acute phosphorus poisoning has been previously outlined⁽²⁾:

1. Supportive measures for shock.
2. Stomach lavage—using oxidizing agents, such as potassium permanganate solutions (1:1000).
3. Purges, such as magnesium sulfate, following lavage. Phosphorus has been discovered in stools three days after its ingestion⁽⁸⁾.
4. Since fats and oils tend to dissolve the poison and to promote its absorption, they are to be avoided. However, it has been shown that some laboratory animals can be saved from acute phosphorus poisoning by the

administration of liquid petrolatum in large amounts. The phosphorus is soluble in this and hence is not absorbed⁽⁹⁾. For this reason, one hundred to two hundred cubic centimeters of liquid petrolatum should be introduced into the stomach.



FIG. 1. J. B.: Forty-first day of illness. X-ray of the upper extremities revealing dense lines of condensation at the distal ends of the radii and ulnae.

5. The acute hepatic insufficiency should be treated with vitamins, especially with those of the B-complex, and vitamin K; dextrose intravenously; and a daily intake of a high carbohydrate, high protein, low fat, liquid diet.

6. Calcium lactate or gluconate, one gram three times daily, may be given.

7. Penicillin should be given in large doses.

8. Isotonic sodium chloride and sodium lactate solutions are given par-

enterally to treat the chemical imbalances of shock, acidosis, and/or dehydration.

9. Blood transfusions should be given as required.



FIG. 2. J. B. Fifty-third day of illness. X-ray of the upper extremities revealing further condensation of the heavy metal at the distal ends of the radii and ulnae.

Although the treatment used in our patient agreed mainly with that outlined above, it differed in several ways. The patient was not lavaged, nor did he receive a cathartic. Liquid petrolatum was not given because at the time we were not cognizant of the experimental work on laboratory animals. An attempt to administer proteins parenterally was abandoned after a reaction of nausea and vomiting. Our patient received one cubic centimeter of crude liver extract intramuscularly daily from the sixth to the seventeenth hospital day, and then every other day until the twenty-

second hospital day. The use of crude liver extract may have been a major factor in aiding recovery.

We would like to emphasize the fact that warm milk was given to this patient shortly after the poison was ingested. Although warm milk is frequently used as a household emetic, it probably does more harm than good in cases of phosphorus poisoning.

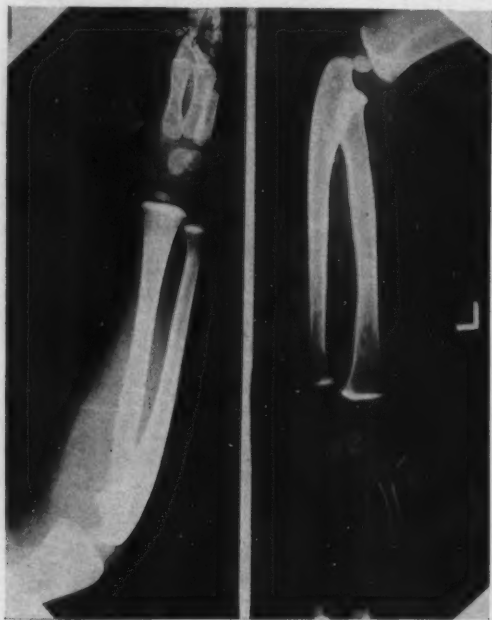


FIG. 3. J. B.: X-ray of the left upper extremity following the traumatic incident. There is no evidence of fracture or periosteal pathology, but the bands of radio density of the distal ends of the radius and ulna are quite evident.

In a review of 250 cases of poisoning admitted to the Children's Hospital, Washington, D. C. from July, 1944, to September, 1948⁽¹¹⁾, one case was due to the ingestion of rat poison containing phosphorus. This was a two year old colored male who died two hours after ingestion. His symptoms and signs consisted of severe hematemesis, abdominal pain, bradycardia, irregular respirations, garlic odor of the breath, hepatosplenomegaly, and lastly, coma. Further review by us failed to disclose any other cases of phosphorus poisoning admitted to the Children's Hospital from September, 1948 until the present time.

At the time of this report, we feel that the patient has recovered from

the acute phase of phosphorus poisoning. The physical examination and most of the laboratory tests are normal. However, since the thymol turbidity test remains elevated, and the urine urobilinogen is greater than normal, the possibility of complete recovery is still questionable. The convalescence must be carefully watched, and excretion tests for liver function evaluation are to be done in the future.

SUMMARY

1. A case of acute phosphorus poisoning with recovery has been reported
2. The signs, symptoms, and treatment of acute phosphorus poisoning have been discussed.
3. The necessity of careful evaluation of the clinical course and laboratory data in relation to the prognosis of the case presented has been emphasized.

N. B. The authors wish to thank Drs. Fernando Leyva and Samuel P. Bessman for their help in preparing this presentation.

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ADDENDUM

The patient was readmitted on April 24, 1950, seventy-one days after he had ingested rat poison containing phosphorus. He had been discharged

from the hospital on March 11, 1950 and had been followed in the Out-Patient Department in the interim. Urine specimens were examined every one to two weeks for bilirubin and urobilinogen. The results are given in the accompanying table.

TABLE 3

Days after Ingestion.....	54	62	71
Icterus Index.....			4 units
Cephalin Flocculation.....			0
Thymol Turbidity.....			2.5 units
Prothrombin Time.....			100%
Blood Phosphorus.....			4.2 mgm. %
Total Protein.....			6.00 gms. %
A.G. Ratio.....			2.5/1
Van den Bergh—			
Direct.....			0.00 mgms.
Total.....			0.25 mgms.
Cholesterol—			
Total.....			185 mgms.
Esters.....			115 mgms.
Urine Bilirubin.....	0	0	0
Urobilinogen (Erich Units).....	1	0	1

On readmission, the interval history was negative except for a fall on April 7, 1950 with resultant trauma to the patient's left arm. X-ray examination at that time showed no evidence of fracture, but revealed the phosphorus bands previously noted. Physical examination on admission revealed an apparently normal child. The skin and sclerae were not icteric. The liver was barely palpable, non-tender, and had a normal consistency.

Laboratory tests and roentgenograms of the long bones were repeated. X-rays showed persistence of the previously-reported phosphorus bands. In addition, a glucose tolerance test and a bromsulphalein excretion test were done so that a more complete evaluation of the liver functions could be obtained. Both of these tests were normal. The results of the other tests are given in tabular form.

TABLE 4

DAYS AFTER INGESTION	HEMOGLOBIN	ERYTHROCYTES	LEUKOCYTES	NEUTROPHILS	LYMPHOCYTES	EOSINOPHILS
	gms.	million		%	%	%
71	14	4.6	6,200	32	64	4

Glucose tolerance and bromsulphalein excretion tests were normal.

The patient was discharged from the hospital on April 27, 1950, seventy-four days after the onset of the illness. The clinical course and laboratory findings, particularly those pertaining to the liver function, indicate that the patient has recovered completely from acute phosphorus poisoning with no residual liver damage.

ADRENAL INSUFFICIENCY IN INFANCY

Paul Kaufman, M.D.

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Case No. 50-2293

D. E. S., a nine day old white male was admitted to Children's Hospital on February 19, 1950 with the chief complaint of vomiting of two day's duration.

The history revealed that the patient was the product of a normal, spontaneous, non-instrumental delivery following an uncomplicated gestation period of eight months. The mother was gravida i, para i. The birth weight was six pounds, four ounces. On the second postpartum day, a yellowish discoloration of the infant's skin was noted. The mother and infant were discharged from the hospital on the fourth postpartum day. For the two days preceding hospitalization, the infant had regurgitated almost every feeding. Regurgitation was not projectile. The bowel movements were normal. The day before admission, the infant's urine seemed darker than usual, however, the diapers were unstained. Soon after birth, the baby was placed on an artificial feeding schedule consisting of one tablespoon of a dried powdered milk preparation to two ounces of boiled water. He would take up to two ounces of this formula every four hours. Water was offered ad libitum between feedings. A private physician added two tablespoons of carbohydrate to the total daily formula because the infant was constipated. The episodes of vomiting closely followed this formula change.

The family history revealed the mother and father to be living and well. There were no other siblings. Syphilis, tuberculosis, and bleeding tendencies were denied and questioning failed to elicit any pertinent familial disorders. The mother had never received any blood transfusions.

The temperature on admission was 96.2 F. and the respiratory rate 50 per minute. The weight was five pounds four ounces. Physical examination revealed a malnourished, dehydrated white male infant with senile facies. Tissue turgor was markedly diminished. The skin was dry and a generalized, yellow pigmentation which was interpreted as icterus was present. The sclerae were icteric. Although moderate dyspnea was present, examination of the lung fields revealed no abnormalities. No masses were palpated in the abdomen. The remainder of the physical examination including the neurological failed to elicit any abnormal findings.

The admission urinalysis was within normal limits. A complete hemogram revealed a hemoglobin of 22 grams; the erythrocytes numbered 5,500,000 per cubic millimeter. There were 18,000 leukocytes per cubic milliliter of which 76 per cent were neutrophils, 22 per cent were lympho-

cytes, and 2 per cent were eosinophils. The carbon dioxide combining power of the serum was 34 volumes per cent. The standard Kahn and Mazzini tests were negative. On examination the mother, father, and infant were found to be Rh positive.

Immediately after admission the patient was placed in an incubator with continuous oxygen therapy. Despite the use of parenteral fluids and gavage feedings, the infant failed to gain weight. Most of the feedings were regurgitated. The course was progressively downhill and on the fourth hospital day cyanosis was marked, respirations became irregular and gasping, and the baby expired.



FIG. 1. Shows the small, thickened, rounded adrenals resting upon the superior poles of the kidneys.

PATHOLOGIC DISCUSSION

The body was that of a well developed and nourished white baby weighing 2.36 kilograms and measuring 46 centimeters long. The skin was slightly icteric and the tissue turgor poor.

The only pathologic findings in the chest were restricted to the right lung which was dark red and felt airless. Cut section confirmed the homogeneous firm dark red appearance. The liver, spleen, and kidneys were grossly congested but otherwise normal.

The adrenals were in normal position. The periadrenal tissue was normal; however, both glands were dark red in color and appeared to be markedly

congested or hemorrhagic. They measured one centimeter in length but were wider than normal. The right gland weighed 0.4 grams, the left 0.3 grams. The sectioned tissue of both was red and hemorrhagic.

Histologically, the right lung showed a diffuse, severe bronchopneumonia. The cellular infiltrate obscured most of the alveolar lumina. The liver, spleen, and kidneys showed moderate congestion.

The adrenal cortical cells, especially those in the zona fasciculata, showed degenerative changes. Many cells had pink staining, finely granular cytoplasm and some showed cytoplasmic distortion with loss of their nuclei.

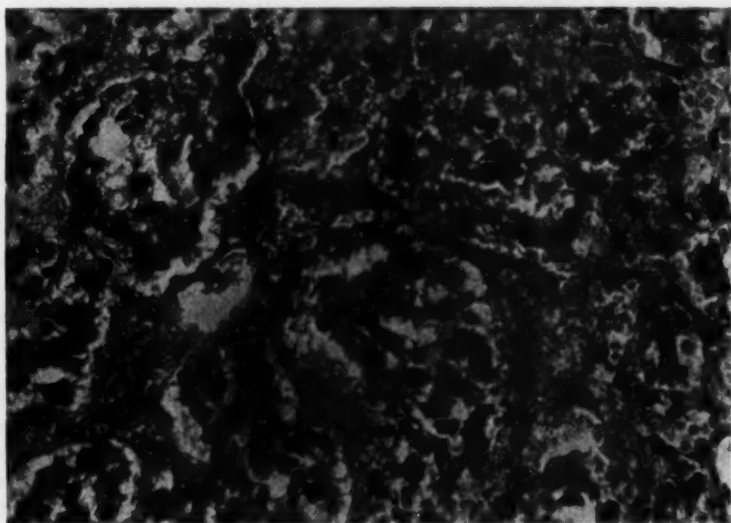


FIG. 2. Shows large numbers of distorted and degenerating adrenal cortical cells with evidence of cytoplasmic vacuolization. An increase of filmy connective tissue along with extravasated erythrocytes are visible between the cortical cells.

Other nuclei showed pyknosis and karyorrhexis. In some areas large pale pink cortical cells with nuclei of increased size and containing one or more nucleoli were present. Marked capillary distention and engorgement with extravasation of large numbers of well formed erythrocytes between the cortical cells were found in some portions of the glands. The cortical cell degeneration was more pronounced in these areas and many cell boundaries were obliterated. A large number of fibroblasts and newly formed connective tissue were present in these areas. In the fibrous tissue mass surrounding the cortex, there were large numbers of small pink staining, well formed

cortical cells. The majority of these cells were discrete but in a few areas they were grouped together in clusters and whorls. Nearby there were large numbers of cells with elongated, dark staining nuclei. The cells of the adrenal medulla were intact but appeared more filmy and vacuolated than normal. This zone was relatively avascular. The changes described were representative of an early degenerative or atrophic process involving mainly the cells of the zona fasciculata of the adrenal cortex being associated with, and possibly secondary to congestion of and hemorrhage into the above portion of the cortex. A reparative process had apparently begun as manifested by fibroblastic activity along with compensatory adrenal hyperplasia. The latter process was evidenced by the adenomatous masses of cortical cells adjacent to the capsule.

DISCUSSION

This case is presented to emphasize the necessity that the physician acquaint himself with the life-sustaining function of the adrenal glands; and to think of the possibility of hypofunction when dealing with infants who during early life present symptoms of protracted gastro-intestinal disturbances, who fail to gain weight, who have an unexplained tendency to dehydration, and who respond unsatisfactorily to accepted therapeutic measures.

Liefmann and Schultz⁽¹⁾ have recently reviewed the functions of the adrenal cortex and the methods of measuring these functions. Secretions of the adrenal cortex are usually considered to comprise three groups:

1. Steroids which predominantly affect carbohydrate metabolism (11-oxysteroids and 11,17-oxysteroids). These substances accelerate conversion of protein to carbohydrate and enhance the utilization of fat (gluconeogenesis). There is a coincident rise in the blood glucose and liver glycogen store as well as marked increase in urate excretion. The more active 11,17-oxysteroids induce lysis of fixed lymphoid tissue, transitory lymphocytopenia, and almost complete disappearance of eosinophilic cells from the circulation. The function of these carbohydrate-regulating steroids may be measured by observing variations in the urinary excretion of 11-oxysteroids, by determining variations in the number of circulating eosinophils, or by determining the urinary uric acid-creatinine ratio.

2. Steroids which have an electrolyte regulating effect, e.g., 11-desoxycorticosterone. Retention of sodium and chloride and increased excretion of potassium are induced. Plasma and extra-cellular tissue volume are coincidentally increased. The measure of the function of these steroids is possible only by indirect methods, e.g., observation of alterations of the mineral content of the urine or sweat, changes in blood composition as determined by hematocrit volumes, and variations in body weight.

3. Steroids especially active as androgens. These are related in chemical structure to testosterone but have an oxygen group at position 11. They cause masculinization with retention of sodium, potassium, phosphorus, nitrogen, and chlorides. The immediate effects of these steroids can be measured only as reflected in slight increase in urinary 17-ketosteroid excretion.

In infancy and childhood disorders of the adrenal glands occur infrequently. A comprehensive classification of these disorders follows:

- I. Acute adrenal insufficiency (adrenal hemorrhage, Waterhouse-Friderichsen syndrome).
 - A. Meningococcemia and other bacterial infections.
 - B. Trauma.
 - C. Fulminating septicemia caused by other organisms.
- II. Addison's disease.
 - A. Tuberculous origin.
 - B. Hypofunction.
 1. Atrophic adrenal glands.
 2. Hypertrophic adrenal glands (dyscorticism).
- III. Hyperadrenocorticism.
 - A. Adrenogenital syndrome (adrenal virilism).
 - B. Cushing's syndrome (basophilic adenoma of the pituitary with secondary adrenal hypertrophy).
 - C. Feminizing adrenal tumors (due to adrenal carcinoma, very rare in children⁽²⁾).
- IV. Pheochromocytoma (neoplasm of the adrenal medulla associated with attacks of hypertension).
- V. Adrenal neuroblastoma.

It is apparent from the protocol that the patient presented was one of a rather severe case of adrenal insufficiency caused by hypofunctioning, atrophic adrenal glands. Snelling and Erb⁽³⁾ in 1935 reported a case of Addison's disease due to atrophy of the adrenal glands in a nine and one-half year old male, and reviewed the literature on this subject. Of the two types of Addison's disease, those cases resulting from tuberculous lesions are more numerous than those in which atrophy of the adrenal glands is the outstanding lesion, a ratio of approximately 3.5 to 1. Brenner⁽⁴⁾ mentioned three possible causes for adrenal gland atrophy:

1. Congenital hypoplasia.
2. Chronic inflammation (including tuberculosis, syphilis, and simple inflammation).
3. Simple atrophy of the cortex and later the medulla.

Adrenal insufficiency in infancy caused by tuberculosis or by bilateral adrenal hemorrhage has been reported by numerous investigators^(5, 6, 7, 8, 9).

However, Jaudon^(10, 11) in 1946, and again in 1948, presented a series of infants with definite related symptoms which responded to the administration of adrenal cortical hormone. He pointed out the similarity between hypofunction of the adrenals in early life and other conditions in infants which result from hormonal imbalance and some apparent difficulty in adjustment of the endocrine mechanism by the infant, e.g., (1) physiologic lactation, menstruation, and involution of the uterus of the newborn due to maternal transmission of placental hormones, (2) hypoglycemia and hyperinsulinism of the newborn, and (3) low calcium tetany apparently due to a physiological hypoparathyroidism. It is probable that hypofunction of the adrenal cortex at times may produce disturbances in the metabolism of young infants.

In these infants there is a negative family history of endocrine dysfunction, an absence of macrogenitosomia and skin pigmentation, and imperceptible amounts of steroids are found in the urine in the majority of cases. Most of the affected infants are males. Jaudon⁽¹¹⁾ has seen only two females with this syndrome.

Symptoms referable to the upper gastro-intestinal tract develop during the neonatal period. Anorexia, regurgitation, and vomiting to some degree are present in all patients. The vomiting may be projectile, and the vomitus usually does not contain bile. Frequently, intestinal patterns and, occasionally gastric waves develop and suggest a high partial, intestinal obstruction. Diarrhea is not a prominent symptom. The course is characterized by periods of improvement alternating with periods of failure to gain and excessive weight loss out of proportion to the amount of food regurgitated. Gradually it becomes necessary to administer parenteral fluids to maintain hydration. It is probable that all degrees of deficiency exist and that the case presented was of the severest type.

The consistent laboratory findings were enumerated by Jaudon⁽¹¹⁾. There is a moderate reduction in the carbon dioxide combining power of the serum. A moderate elevation of the non-protein nitrogen is present. A normal to low sodium chloride is found in the serum in the presence of a low blood volume. Chlorides are abundant in the urine. In some cases the serum potassium may be elevated, and moderate increase in the urinary output of 17-ketosteroids may be found in a few cases. The last two determinations are inconstant features of this syndrome.

The differential diagnosis at times may be extremely difficult since degrees of adrenal deficiency are probable and symptoms, therefore, vary from mild to severe.

1. Early in the disease, the patient with mild symptoms may be considered to have pylorospasm or to be a feeding problem. With the appearance of rapid weight loss and tendency to dehydration, the diagnosis is simplified.

2. High, partial intestinal obstruction must be considered in those cases in which gastric waves, intestinal patterns, and slow emptying time of the stomach are present. However, in the syndrome of hypofunctioning adrenal glands gastric waves or intestinal patterns when present are never persistent. Too, the excretion of large amounts of chlorides in the urine during periods of dehydration is rarely, if ever, seen in uncomplicated cases of pyloric stenosis.
3. The clinical manifestations may be confused with congenital renal defects. In the syndrome under discussion, the carbon dioxide combining power is only moderately decreased. The elevated non-protein nitrogen is associated with hemoconcentration but, in most cases, can be promptly lowered when hydration is established. Even in the presence of a low blood volume, the serum sodium chloride is normal or reduced. Pyelography reveals no abnormalities, blood pressures are normal, and no eyeground changes are present.
4. Macrogenitosomia cannot be differentiated in the first few weeks when there are no signs of abnormal genital development. The signs of virilism in patients with hyperplasia of the androgenic zone associated with adrenal insufficiency appear at six months of age. If large amounts of 17-ketosteroids are continuously excreted in the urine, precocious sex development will probably occur.
5. The young age of these patients, the lack of skin pigmentation, and the failure to demonstrate deficiency in carbohydrate metabolism should cause no confusion between this syndrome and Addison's disease.

Jaudon^(10, 11) has presented suggestive evidence that these patients respond dramatically to the parenteral administration of adrenal cortical extract or desoxycorticosterone acetate. The intravenous administration of adrenal cortical extract dissolved in normal saline is recommended for the treatment of shock where immediate response is imperative. There is no evidence that it is superior to the steroid and the benefit obtained from its use is probably due to the presence of the desoxycorticosterone fraction. The dose of desoxycorticosterone acetate should be regulated according to the individual need at that particular time. An adequate dose for most patients during the period of regulation is approximately 2.0 milligrams daily. The steroid without added salt produces only temporary relief and 2.0 grams of sodium chloride should be given daily. At a subsequent date, regulation may be possible with the use of sublingual Cortate. The recommended dosage should be maintained until the time when it can safely be decreased and eventually eliminated.

In 1948, Forsham and his co-workers⁽¹²⁾ first described the use of the direct eosinophil count in the estimation of adrenocortical function. The levels of circulating eosinophils are intimately related to the activity of the adrenal

cortex. Under conditions of stress, the pituitary releases adrenocorticotrophic hormone (ACTH); ACTH in turn (in the presence of normally functioning adrenal glands) stimulates the adrenal cortex and results in a release of steroid hormones in large quantities. Of these steroids, the 11, 17-oxysteroids produce a fall in eosinophil levels⁽¹³⁾. In an extensive study, Roche et alii⁽¹⁴⁾ indicate that the finding of a normal or high eosinophil level during the first twenty-four to forty-eight hours after an operation suggests adrenocortical insufficiency. The circulating eosinophil level is therefore of probable value in determining adrenocortical activity in various pathological states. In a practical application of these principles, Falloon and his associates⁽¹⁵⁾ treated a 17 year old white female with the diagnosis of acute adrenal insufficiency (Waterhouse-Friderichsen syndrome). Adequate replacement therapy was controlled by repeated eosinophil counts. It is of interest to speculate on the possible application of these new ideas to the syndrome of hypofunctioning, atrophic adrenal glands in infancy. Theoretically, the circulating eosinophil level in such infants should be normal or elevated because of the deficiency in the hormonal secretions from the cortex. The administration of one dose of ACTH to such a patient should produce no response, i.e., there would be no effect on the circulating eosinophil level. Replacement therapy could then be controlled by repeated eosinophil counts when whole adrenocortical extract containing 11, 17-oxysteroids is utilized.

SUMMARY

1. A case of adrenal insufficiency due to hypofunctioning, atrophic adrenal glands occurring in a newborn has been presented.
2. A review of the physiology of the adrenals, a classification of adrenal disorders, and the syndrome of hypofunction of the adrenal glands in early life has been made.
3. The possible role of circulating eosinophil levels in the diagnosis and treatment of this syndrome has been speculated upon.

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CLINICO-PATHOLOGICAL CONFERENCE

Directed by: E. Clarence Rice, M.D.

Assisted by: William M. Crowell, M.D.

Francis J. Troendle, M.D.

By Invitation: Joseph M. LoPresti, M.D.

William M. Crowell, M.D.

M. E. C. 34-6156

M. E. C., a four year old white female, was admitted with a history which began six weeks before admission. At that time she developed a sore throat and a partial paralysis of the right face, arm, and leg. The right corner of the mouth could not be "pulled up" and the right arm and leg were weak, the latter causing the child to limp. The sore throat cleared promptly and the paralysis gradually improved but did not disappear completely.

Twelve days before admission, while eating lunch, the patient complained of inability to see. When put to bed, she thrashed about wildly, chewed the bed linen, screamed with pain, and lost consciousness. Her right arm and leg became rigid and were held in extension. Later it was noticed that the extremities on the right occasionally flexed slowly but usually were "straight and stiff." The child regained consciousness but was very "dull" mentally. She ate very little. In the next few days she became more and more stuporous and lost consciousness completely the day before admission. At this time hospitalization was advised.

The patient was delivered at home. Birth was at term and forceps were used. She weighed seven and one-half pounds. Development was normal and nutrition had been adequate. There was a history of whooping cough at five weeks, chicken pox at two years, and measles at three years. During the first year of life she was seen at Episcopal Hospital where a diagnosis of xerophthalmia of the right eye was made and vitamin A recommended. A fall on the back of the head without loss of consciousness one year previously preceded the present illness.

The family history was not contributory.

Physical examination on admission revealed a pale child in coma. Occasional purposeless movements of the upper extremities, particularly the right, were observed. The temperature was 102.6 F. rectally and the systolic blood pressure was 110 millimeters. Pulse and respiratory rates were not recorded. There were numerous petechiae on the palms and soles. Over the body, larger erythematous areas which did not blanch on pressure were present. Those were thought to be hemorrhagic.

The head appeared normal in size and shape. The eyes were semi-dilated and fixed. The right pupil was largely occluded by a dense corneal scar.

The vessels seemed dilated and tortuous and the disk blurred with an exudate, but there was no obvious hemorrhage. The disk was almost obliterated; there were three diopters of choking and the veins were full.

The ear drums were normal except for several petechiae. The mouth and throat could not be examined because the jaws were shut tightly. Heart and lungs were negative; no masses or organs could be felt in the abdomen. There was no lymphadenopathy. The lower extremities were rigid and extended. The deep reflexes were exaggerated and the Babinski was positive bilaterally. Kernig's sign was suggestively positive and the Brudzinski was negative. Hemogram revealed a hemoglobin of 11 grams per 100 milliliters, erythrocytes 3,080,000 per cubic millimeter, and leukocytes 10,800 per cubic millimeter with 87 per cent neutrophils. Twenty-six milliliters of clear, colorless fluid was removed from the lumbar spine under apparently increased pressure. It was normal in cellular and chemical content.

Shortly after the lumbar puncture, the patient broke out with numerous red patches over the body, became cyanotic, and stopped breathing. The pulse was then noted to be rapid and thready. She was given artificial respiration and stimulants, but failed to respond and was pronounced dead four hours after admission.

DISCUSSION

Joseph M. LoPresti, M.D.: In approaching the problem which is presented at a Clinico-Pathological Conference, there are three principles which I believe should be followed in an attempt to arrive at the most logical diagnosis: first, to obtain a clear, concise picture of what the patient's clinical history presents; second, to explain, if possible, the entire clinical picture on the basis of one diagnosis; and third, in the event that the clinical picture fits two or more diagnoses, to select the most common condition as the most likely diagnosis.

The case presented is that of a four year old white female with a history of illness of six weeks' duration which, in summary, demonstrates the following salient features:

1. Hemiplegia of sudden onset with subsequent clearing.
2. Generalized convulsions just prior to admission.
3. Coma.
4. Presence of fever.
5. Skin lesions (petechial and purpuric).
6. Presence of increased intracranial pressure.
7. Retinal hemorrhages and exudates.
8. Signs of meningeal irritation with a normal spinal fluid.
9. Sudden exitus with the appearance of cyanosis, purpura, and shock.

There are two details in the past history which can be summarily dismissed.

1. The history of head injury one year before the present illness.
2. Xerophthalmia of the right eye.

It would be unusual for a head injury to produce symptoms after such an interval has passed. As to the latter, in avitaminosis A there is a metaplasia of the epithelial cells of the cornea. This leads in succession to: xerosis, Bitot's spots, xerophthalmia, and finally keratomalacia. The last two conditions may be irreversible and result in permanent scarring of the cornea (an explanation of the right corneal scar).

There are two conditions which must always be considered in the differential diagnosis of any condition in childhood which presents such a bizarre picture as the case under discussion. The first of these is syphilis. In order for syphilis to produce the clinical picture which this patient demonstrated, there would have to be an involvement of the central nervous system. The spinal fluid was normal. Too, the absence of other stigmata of congenital syphilis tends to rule out this diagnosis. The second is tuberculosis. In order for tuberculosis to produce the signs and symptoms in this patient, it would most likely have to be of the miliary type and also involve the central nervous system. The absence of splenomegaly and hepatomegaly and the normal spinal fluid are all points against the diagnosis of miliary tuberculosis.

I have included conditions which may produce some or all of the features in this case and they have been divided into four groups:

1. Neoplasms,
2. Infections,
3. Blood dyscrasias, and
4. Miscellaneous conditions.

I. *Neoplasms*: (Primary Intracranial or Metastatic to the Brain)

- A. Primary intracranial neoplasms are not infrequently encountered in childhood. Twenty-five per cent of these neoplasms are supratentorial, while 75 per cent are infratentorial and located in the posterior fossa. The most commonly encountered infratentorial neoplasms in childhood are the astrocytoma and the medulloblastoma. Such primary intracranial lesions usually produce signs of increasing pressure such as headache and vomiting at first. Quite frequently signs of cerebellar irritation such as uncertainty of gait and nystagmus appear later. Focal symptoms occur late in the disease. A diagnosis of primary intracranial neoplasm leaves the skin manifestations unexplained.
- B. Metastatic Neoplasms to the Brain: The most commonly encoun-

tered neoplasm in childhood which metastasizes to the skull is the neuroblastoma. While a neuroblastoma may arise anywhere in the sympathetic nervous system, the greater majority arise in the adrenal gland. These tumors grow rapidly and metastasize early. They metastasize to the liver, long bones, and skull. Frequently the earliest signs are the presence of a palpable abdominal mass or an enlargement of the liver. These patients rapidly become anemic and cachetic.

- C. Recently at one of our conferences, we had a case presented of an adenocarcinoma of the kidney, which had metastasized to the skin and to the brain. The primary lesion was much smaller than the metastatic lesion. No abdominal mass was palpable and the earliest symptoms in this case were those which were referable to the central nervous system.

II. Infections:

- A. Brain Abscess: Brain abscess in children usually develops from direct extension of an infection of the mastoids, middle ear, or sinuses. Infrequently, they may be hematogenous in origin. In such cases, the primary lesion is usually pulmonary or pleural and the hematogenous lesions to the brain are usually multiple. The symptomatology of brain abscess in childhood is most frequently divided into three stages:
1. The symptoms are those referable to the primary infection (mastoiditis, otitis, sinusitis, etc.).
 2. After a short period of time these symptoms abate and the patient becomes asymptomatic, for a period which may be as long as two to four weeks.
 3. Then the symptoms of increased intracranial pressure appear with a return of fever. Depending on the location of the abscess, the patient finally develops focal symptoms; the spinal fluid may never show any changes but usually there is a moderate increase in the number of cells and in the protein content.
- B. Meningitis: This diagnosis may immediately be dismissed by the normal spinal fluid in this patient.
- C. Nephritis: Nephritis in childhood may be acute or chronic. Ninety per cent of patients with acute nephritis get well and never have any sequelae. The presence of hypertensive retinopathy, i.e., hemorrhages and exudates, is unusual in acute nephritis. When a fatal outcome is encountered it is most frequently due to cardiac involvement.

The greater percentage of children with chronic glomerulo-

nephritis do not give a history of a preceding acute onset. This condition is characterized by remissions and exacerbations. During exacerbations, there are urinary changes, hypertension, central nervous system manifestations, and characteristic changes in the blood chemistry. Hypertensive retinopathy occurs commonly. The prognosis is poor; the patient dies as a result of a cerebral hemorrhage or uremia. In the absence of sufficient data in the case under discussion we cannot categorically rule out chronic nephritis as the cause, but we can presume that it is unlikely.

- D. **Bacterial Endocarditis:** Bacterial endocarditis may be acute or subacute. Acute bacterial endocarditis is most frequently caused by the streptococcus and pneumococcus. Only occasionally does it occur as a complication of congenital or organic heart disease. The patient is toxic; the fever is high and usually remittent. Murmurs are absent or distant. Blood cultures, when repeated, are positive and a leukocytosis is present. Skin manifestations may occur, but retinal changes are not seen. The course is fulminating and invariably fatal. Subacute bacterial endocarditis usually has a protracted course and is caused by *Streptococcus viridans*. Often it develops at the site of congenital or valvular defects. Hemiplegia and central nervous system involvement, as a result of embolic phenomena, are not unusual. Splenomegaly, anemia, and leukocytosis are common concomitant features.
- E. **Septicemia Including Meningococcemia in Childhood:** Septicemia, particularly that caused by the meningococcus is not infrequently encountered. The temperature is elevated and remittent in type. Blood cultures are positive. Skin manifestations, such as petechiae and purpura, may be seen. A leukocytosis is usually seen. Meningococcemia may be complicated by bilateral adrenal hemorrhage. This condition is known as the Waterhouse-Friderichsen Syndrome and is characterized by hyperpyrexia, cyanosis, shock, massive purpura, and sudden death.

III. *Blood Dyscrasias:*

- A. The severe anemias are ruled out by the hemogram in this patient.
- B. **Purpura hemorrhagica fulminans** may occur in childhood. It is characterized by petechial hemorrhage and ecchymosis into the skin. There is bleeding from the nose, mouth, genito-urinary tract, and gastro-intestinal tract. Hidden hemorrhages may be present and the central nervous system may be the site of widespread hemorrhages. The patient dies shortly after the onset. This diagnosis cannot be ruled out in this case.

- C. Leukemia in childhood may have many diversified appearances. It is not unusual to encounter an acute onset with purpura and central nervous system manifestations. However, the absence of lymphadenopathy, splenomegaly, and hepatomegaly are points against the diagnosis of leukemia.

IV. *Miscellaneous Conditions:*

- A. Liver pathology, such as an abscess, neoplasm, or infection may produce some of the symptoms that this patient presents. We have seen one case of diffuse hemangioma of the liver in a two year old white male in which the pathology was so extensive that interference with liver function was produced. In this case, there was a prothrombin deficiency of such marked degree that hemorrhagic phenomena were present. This patient died of a massive intracranial hemorrhage.
- B. In 1866 Kussmaul and Maier first described the condition which they named periarteritis nodosa. The cause of this disease is still unknown. Keith and Bagginstoss in 1941 summarized the medical literature and were able to locate forty-two cases of periarteritis nodosa in children to which they added two of their own cases. In the period between 1866 and 1932 only twenty-three cases were recorded in children, while in a six-year period between 1933 and 1939 there were twenty-one cases recorded. The diagnosis of periarteritis nodosa was made antemortem in only 16 per cent of these cases. The presence of: (1) prolonged septic temperature without explanation, (2) symptoms in various parts of the body which can be related to arterial occlusions, and (3) the appearance of nodules under the skin should make one suspect the diagnosis. Many conditions may be simulated during the course of this disease and some of the suspected diagnoses in this series of cases were:

1. Purpura hemorrhagica
2. Typhoid fever
3. Miliary tuberculosis
4. Meningitis
5. Brain tumor
6. Acute intra-abdominal crises
7. Rheumatic fever
8. Nephritis.

The symptomatology is protean. Fever was present in 86 per cent of these patients and leukocytosis in 63 per cent. There were generalized convulsions in 38 per cent and anemia in 34 per cent. A purpuric rash occurred

in 27 per cent of the children and meningeal signs occurred in 7 per cent. Interestingly enough, palpable nodes were present in only 2 cases. Patients with hemiplegia and retinal hemorrhages with exudates have been recorded. Periarteritis nodosa is a disease of the small arteries and arterioles and the lesions may occur in any organ. In the order of occurrence the renal, coronary, mesenteric, hepatic, and central nervous system vessels are most commonly involved. At necropsy, gross lesions are not often prominent. However, nodules, aneurysms, and thrombosis may be seen along the smaller blood vessels. Arkin has divided the histopathology into four stages:

1. Necrosis of the inner media of the arterioles and of the outer media of the larger arteries. Edema and fibrous exudate are present.
2. The stage of exudative inflammation. The media and adventitia are seats of massive accumulation of polymorphonuclears, eosinophiles, lymphocytes, and plasma cells. There is a proliferation of the intimal connective tissue. Complications occur towards the end of this stage (aneurysm, thrombosis, and hemorrhage).
3. The stage of regenerative and proliferative processes. There is organization of thrombi and granulation tissue.
4. Formation of scar tissue and healing.

In the prognosis, death results from complications which may occur from four hours to four and one-half years after the onset of illness. Infarction and necrosis produce sudden exitus when they involve the bowel, heart, or brain. Renal insufficiency and pneumonia are complications which frequently result in death.

In conclusion, while periarteritis nodosa is a most attractive likelihood, I must adhere to the third principle and select purpura hemorrhagica fulminans as the most logical diagnosis because of its more common occurrence. Following these, leukemia, bacterial endocarditis, and septicemia are the possibilities which have not been entirely ruled out.

PATHOLOGIC DISCUSSION

E. Clarence Rice: M.D.: Necropsy in this case was limited to the head.

The bones of the skull were thinner than normal on the right. The dura was normal. On exposing the brain the convolutions were found to be somewhat flattened, more marked on the left side. The surface of the brain appeared drier than usual. The consistency of both hemispheres seemed normal. The optic chiasm, the sella turcica, and pituitary were normal grossly. Upon cutting the tentorium cerebelli, considerable cerebrospinal fluid welled up from below. A portion of the cerebellum was found to have been forced down through the foramen magnum. The cerebellum was of normal consistency. An area in the brain stem measuring 1.5 x 0.75 centi-

eters, apparently representative of an accumulation of bloody fluid, appeared to be limited externally only by the pia-arachnoid.

After fixation, the brain was sectioned through the longitudinal fissure. The right lateral ventricle was dilated and contained blood-tinged fluid. The left was compressed from beneath and laterally by a large tumor mass, the tip of which projected slightly near the juncture of the left crus and temporal lobe, a portion of the crus having been destroyed. From this point, the mass extended upward and outward, occupying a space measuring $7.0 \times 4.5 \times 3.5$ centimeters. It appeared to arise at a point anterior to and above the fourth ventricle. The tumor occupied the greater portion of the left parietal lobe and a portion of the occipital lobe, extending to

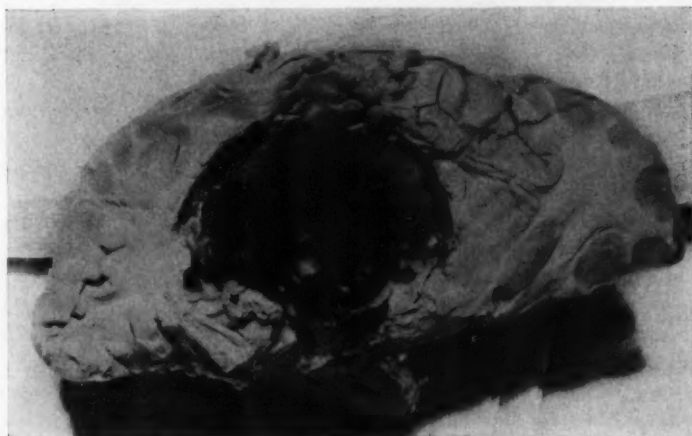


FIG. 1. M. E. C. Sagittal section of the left hemisphere showing hemangioma which has ruptured into the cortex.

within 7 centimeters of the anterior surface of the frontal lobe and between 2.5 and 3.5 centimeters of the surfaces of the parietal and occipital lobes. Only 5 millimeters of tissue separated it from the left lateral ventricle which it compressed.

The tumor was dark red and hemorrhagic, being relatively soft and rather fluctuant. There was no definite capsule, although one portion was covered by grayish fibrinous material which seemed to be representative of an organized clot. The adjacent brain tissue was rather soft and discolored anteriorly, elsewhere it was relatively firm. Grossly it was impossible to determine if the tumor mass was neoplastic or merely represented a partially organized clot.

Microscopic examination revealed many blood vessels of irregular outline

and arrangement which were frequently lined by broad, somewhat irregular endothelial cells. Numerous areas of hemorrhage were noted. In many places plasma cells, lipoid containing cells, and phagocytic cells containing erythrocytes and leukocytes were observed. The lesion was considered to be a cerebral hemorrhage in an area of unusual vascularity, possibly being classed as a hemangioma. There was no evidence of malignancy. Diagnosis: Hemangioma (?) with hemorrhage and inflammatory reaction.



FIG. 2. M. E. C. Left hemisphere showing hemorrhage into the cortex compressing the ventricles.

Unfortunately a complete autopsy was not performed and the short period of hospitalization did not allow an adequate work-up. The blood examination indicated a moderate anemia, with an inflammatory reaction suggested by a moderate leukocytosis with increase in the number of polymorphonuclears. No reduction in the number of platelets was reported. The spinal fluid was under increased pressure but was normal otherwise. With the information which we have at hand, we can assume that the initial hemorrhage in the brain occurred twelve days before admission to the hospital. Subsequent bleeding probably occurred.

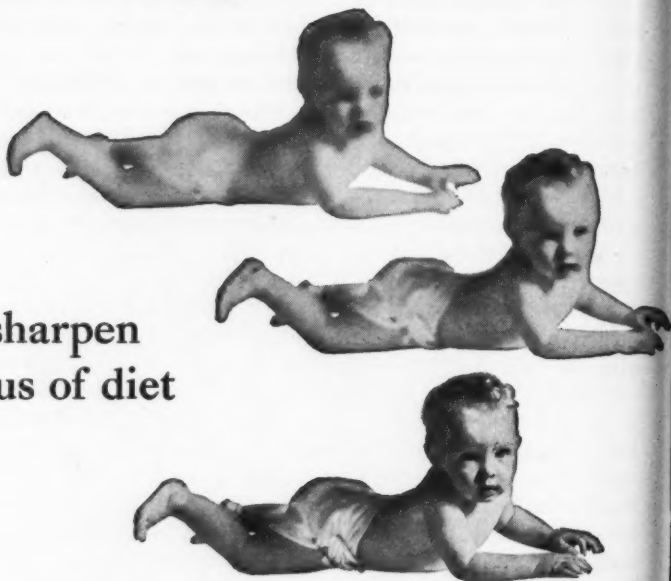
In view of our inadequate information in this case we can only discuss generally the most common causes of sudden evidence of brain pathology

such as seen in this patient. Brain tumor would certainly be one condition which would have to be ruled out. Medulloblastoma, astrocytoma, and craniopharyngioma are the most common tumors we have seen but ordinarily the location of the first two is such as to indicate involvement of the cerebellum rather than the cerebral hemispheres. The symptoms at onset are usually less sudden than in this patient. Cerebral vascular accidents are not common in children but are usually associated with an infection. Massive hemorrhage into the ventricles is sometimes seen as a complication of tuberculous meningitis and a cerebral thrombosis following tonsillectomy can be recalled. Rupture of an aneurysm of one of the cerebral blood vessels is usually followed by rather sudden unconsciousness and death. Embolic phenomena, involving the brain, are seen secondary to endocarditis and septic embolism from abscesses in various parts of the body. They are also noted following tonsillectomy or tooth extraction. Onset may be sudden or quite slow and indefinite in nature. Thrombocytopenic purpura, idiopathic, or secondary to a disease such as leukemia may give rise to a symptom complex such as this child had. We do not have sufficient information to prove this diagnosis. We know that hemangioma of the brain and hemangiomas of other organs of the body, particularly the liver, are sometimes associated. If there had been sufficient involvement of the liver to alter the clotting mechanism, the petechiae and hemorrhages seen in this patient might be accounted for. Hemangiomas of the brain in children are most commonly found in the cerebellum. Angiomatous malformations of the retina associated with hemangioma of the cerebellum is known as Lindau's disease. The fact that such conditions occur indicate some derangement in the formation of blood vessels during embryonic life.

In view of the fact that the pathologist could not satisfy himself that the tumor was a hemangioma, we cannot come to a definite diagnosis in this case. In my opinion hemangiomas of the brain or thrombocytopenic purpura hemorrhagica are the most probable diagnoses.

Finally, I would call your attention to the matter of the spinal puncture which was performed on this patient. You will recall that 26 milliliters of fluid was withdrawn under increased pressure; that the patient's condition rapidly became worse after this; and that she died four hours later. At necropsy a portion of the cerebellum was found to have been pushed down through the foramen magnum. It seems quite likely that the removal of this quantity of cerebrospinal fluid by spinal puncture contributed to the death which followed shortly thereafter. I would remind you of the danger to life in the withdrawal of spinal fluid in a patient with a brain tumor or who has increased intracranial pressure. If examination of fluid is deemed necessary, only the smallest quantity needed for essential examinations should be removed under the greatest care.

Flexible Formula



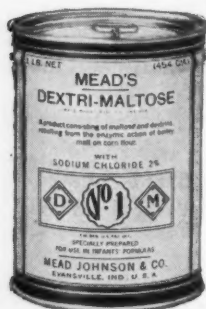
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